

Targeted therapy in recurrent or metastatic head and neck carcinoma

Abstract

This review article is trying to high light the current evidence to support the use of targeted therapy for the best management practices for patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Platinum based chemotherapy is the cornerstone of palliation for patients with R/M HNSCC. Platinum doublets induce higher response rates at the cost of toxicity, but do not demonstrate a survival advantage. EGFR inhibitors, including monoclonal antibodies and tyrosine kinase inhibitors, have achieved only modest success in R/M HNSCC. Immunotherapy represents an attractive treatment strategy for R/M HNSCC, with promising preliminary results. Despite therapeutic advances, prognosis remains poor for patients with R/M HNSCC, illustrating the importance of identifying predictive biomarkers and finding ways to overcome mechanisms of resistance.

Keywords: targeted therapy, head and neck carcinoma, metastatic or recurrent disease

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Abbreviations: R/M, recurrent and/or metastatic; HNSCC, head and neck squamous cell carcinoma; FU, fluorouracil; PFS, progression-free survival; OS, overall survival; EGFR, epidermal growth factor receptor; TGF- α , transforming growth factor-alpha; TKI, tyrosine kinase inhibitors; mAb, monoclonal antibodies; ACU, area under the concentration; PD 1, programmed death 1; IC, investigator's choice

Introduction

Most often, patients with head and neck squamous cell carcinoma (HNSCC) present with locally advanced-stage disease, comprising stage III to IVB disease.^{1,2} It is estimated that up to 60% patients develop local failure and up to 30% have risk of distant failure.^{2,3} Despite therapeutic advances and multimodality treatment, prognosis remains poor for patients with recurrent or metastatic HNSCC. In most of the series the median survival of patients with recurrent or metastatic head and neck squamous cell cancer is ranging from six to nine months only.^{4,5} Management of these patients depends on their general condition, comorbidities, initial treatment plan, and time interval to recur. Salvage surgery and/or re-irradiation are options for patients with local recurrence and many series has demonstrated prolonged survival.⁶⁻⁸ Systemic therapy is indicated in conjunction with best supportive care for most patients with metastatic or advanced recurrent head and neck cancer. In this subgroup, patients undergoing palliative systemic therapy for inoperable locally recurrent disease have prolonged disease-free survival compared with patients with metastatic disease.⁹ The choice of a systemic regimen is influenced by whether patients have received systemic agents as part of their initial management plan, time to relapse and performance status of the patient.

Treatment options include single agent therapy and combination regimens using either conventional cytotoxic chemotherapy and/or molecularly targeted agents, combined with best supportive care. Initially Methotrexate and bleomycin were in use and by 1980s Platinum-based chemotherapy became the backbone of treatment.

Later it was found that platinum doublets induce better response rates than single agents at the cost of increased toxicity, but they did not demonstrate a survival advantage. The regimens of platinum combined with fluorouracil (FU) or a taxane showed 30% response rate, median progression-free survival (PFS) of 3 to 4 months, and median overall survival (OS) of 6 to 8 months.^{10,11} Triplet cytotoxic regimens were subsequently tested, again survival was not improved and toxicity was considerably more compared to doublets.¹²⁻¹⁴ Later targeted therapy were developed, when added to cytotoxic chemotherapy, they resulted in a median survival time of 10 months.¹⁵ This article will review the current evidence for the use of targeted agents in recurrent or metastatic head and neck cancer.

EGFR inhibitors

Epidermal Growth Factor Receptor (EGFR) remains the most robustly studied and proven marker in head and neck cancers. Epidermal growth factor receptor (EGFR) protein expression is detected in 90% of all HNSCC tumors.¹⁶ EGFR is a 170-180kd trans membrane glycoprotein tyrosine kinase receptor. It binds Epidermal growth factor (EGF), Transforming growth factor-alpha (TGF- α), and other regulating proteins. Activation of EGFR results in a complex cascade of signaling pathways that influence normal cellular proliferation and differentiation which lead to strong mitogenic activity. High levels of EGFR protein expression is associated with decreased survival, resistance to radiotherapy, loco regional treatment failure, and increased rates of distant metastases.¹⁶ EGFR inhibitors include monoclonal antibodies (mAb) that block the extracellular ligand-binding domain, and small molecule inhibitors (Tyrosine kinase inhibitors -TKI) that inhibit activation of the intracellular cytoplasmic tyrosine kinase.

Cetuximab is a monoclonal antibody to the extracellular domain of EGFR and inhibits its downstream actions via multiple mechanisms. In March 2006, the US Food and Drug Administration granted approval for the addition of cetuximab to radiation therapy in locally or regionally advanced SCCHN or as monotherapy for patients with platinum-refractory, recurrent or metastatic (RM) SCCHN. This

approval was based on a randomized phase III trial⁴ and a single-arm phase II trial.¹⁷ Bonner et al.⁴ demonstrated that the combination of cetuximab and radiation was superior to radiation alone in patients with stage III/IV SCCHN with statistically significant improvements in locoregional control (24.4 v 14.9 months; $P=.005$) and overall survival (OS; 5-year OS, 45.6% v 36.4%; $P=.018$).

Table 1 Phase II trials addressing role of cetuximab in R/M SCCHN

Author	Phase	Patients	Treatment	Results
Hitt ¹⁹	II	46(35 evaluable)	Cetuximab/Paclitaxel	CR 24% PR 36%
Vermorken ¹⁸	II	103	Cetuximab	Median OS 178 days
Herbst ²⁰	II	155	Cetuximab/Platinum	11.50%
Baselga ²¹	II	96	Cetuximab/Platinum	183 days

From the phase II trials, it was clear that the combination of cetuximab and platinum chemotherapy is a good option and well-tolerated approach to the treatment of patient population with platinum-refractory recurrent or metastatic SCCHN for whom there are no recommended standard therapeutic options. An additional indication for cetuximab was granted by the US Food and Drug

An open-label, single-arm trial evaluated the efficacy of cetuximab in 103 patients with RM SCCHN who experienced disease progression on platinum-based therapy and demonstrated an objective response rate of 13% with a median duration of approximately 4 months.¹⁸ List of phase II trials addressing role of cetuximab in recurrent or metastatic setting is summarized in Table 1.

Administration in November 2011 for the treatment of recurrent or metastatic SCCHN in combination with platinum-based therapy and fluorouracil or metastatic SCCHN following progression with platinum-based chemotherapy. It was based on phase III trials mentioned in Table 2.

Table 2 Phase III trials addressing role of cetuximab in R/M SCCHN

Author	Phase	Patients	Treatment	Results
Vermorken ¹⁵	III	220	Platinum/FU	Median OS
		222	Platinum/FU/cetuximab	7.4 months 10.1 months*
		57	CDDP/cetuximab	Median OS
Burtneess ²²	III	60	CDDP	9.2 months
				8 months

EGFR-targeted therapy for first-line treatment of recurrent or metastatic (R/M) CCHN

In the phase III EXTREME trial, 442 Patients with recurrent or metastatic head and neck cancer were assigned to platinum/5FU with or without cetuximab¹⁵. Patients received either cisplatin [100mg/m² on day 1] or carboplatin [area under the concentration x time curve

[AUC] of 5 day 1)] plus fluorouracil (1000mg/m² per day for four days) every three weeks with or without cetuximab (400mg/m² for the initial dose, followed by subsequent weekly 250mg/m²). Chemotherapy was given for a maximum of six cycles, and cetuximab was continued as maintenance until disease progression or toxicity. Overall, 39 percent of patients had received systemic chemotherapy at least six months prior to randomization as part of their initial definitive management (Table 3).

Table 3 Results of EXTREME trial is summarized below

	Cetuximab+ Platinum/5-FU (N=222)	Platinum/5-FU (N=220)
Median age, yrs (range)	Median age, yrs (Range)	57(33-78)
Male/female, %	89/11	89/11
Loco-regional recurrence	54%	54%
Metastasis	46%	46%
Primary metastatic disease, %	8	7

The trial concluded that chemotherapy plus cetuximab significantly prolonged overall survival compared with chemotherapy alone (median 10.1 versus 7.4 months, $P=0.04$). Significant improvements were also seen in the progression-free survival and objective response rates (median 5.6 versus 3.3 months and 36 versus 20 percent, respectively). The low numbers of patients with p16 and/or HPV positive tumours treated with chemotherapy plus cetuximab trended toward better progression-free survival, overall survival, and response rate than those who received chemotherapy alone. The overall incidence of severe (grade 3 or 4) adverse events with the cetuximab regimen was not significantly increased compared with chemotherapy alone (82 versus 76 percent).

5 year follow up data of Extreme trial²³ showed consistent results. It was found that a total of 100 patients in the cetuximab arm who had at least stable disease received cetuximab monotherapy until disease progression or unacceptable toxicity, with a median treatment duration of 29.9 weeks. Thirty-one (14%) patients in the cetuximab arm and 25 (11%) in the CT arm of the intention to treat population were deemed long-term survivors (>2 years). Retrospective analysis of the trial showed that p16 and HPV status have prognostic value in recurrent or metastatic SCCHN and survival benefits of chemotherapy plus cetuximab over chemotherapy alone are independent of tumour p16 and HPV status.²⁴

Likewise, Panitumab was tested in phase III trials in patients with recurrent or metastatic setting. In the SPECTRUM phase III trial, 657 patients were treated with cisplatin plus 5-fluorouracil, with or without Panitumumab.²⁵ The primary objective of the trial was overall survival and there was a statistically non significant trend toward increased overall survival with the addition of Panitumumab (median 11.1 versus 9.0 months, $P=0.1403$). It improved progression-free survival and had an acceptable toxicity profile. HPV status was available by p16 immunohistochemistry in 67% of patients and retrospective analysis showed benefit in terms of progression-free and overall survival for the p16 negative patients. However, this study is difficult to interpret because of the low cut-off used to define p16 positivity, the inclusion of non-oro-pharyngeal p16 positive patients in the analysis, and the poor correlation between p16 positivity and the presence of HPV DNA in other studies (Table 4).

Table 4 Spectrum trials and Results

Spectrum Trial	Results
n=657	Local PFS-Improved
met/rec HNSCC	OS-not significant
CDDP+5FU+/-Panitumumab	Benefit-HPV negative patients

The programmed death 1 (PD-1) inhibitor pembrolizumab demonstrated a clinically significant 24.8% overall response rate in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), supporting further study of pembrolizumab as anticancer therapy for advanced head and neck cancers.²⁶

Targeted therapy for second-line treatment of recurrent or metastatic SCCHN

Nivolumab is the first immune checkpoint inhibitor to demonstrate improved OS in a randomized controlled trial in platinum-refractory R/M SCCHN compared to investigator's choice (IC) chemotherapy.²⁷ The drug is a fully human IgG4 anti-PD-1 monoclonal antibody.

patients aged ≥ 18 yr with R/M SCCHN and ECOG PS 0-1 were randomized 2:1 to nivolumab 3 mg/kg q2w (until PD or toxicity) or single-agent chemotherapy (MTX, docetaxel, or cetuximab). 361 patients were randomized, 240 to nivolumab and 121 to single agent chemo. The median overall survival was 7.5 months for nivolumab (95% confidence interval 5.5 to 9.1) versus 5.1 months (95% CI, 4.0 to 6.0) for patients who received IC chemotherapy. Overall survival was significantly longer with nivolumab than with standard therapy with significant P value (hazard ratio for death, 0.70; 97.73% CI, 0.51 to 0.96; $P=0.01$). Treatment-related adverse events of grade 3 or 4 were notably low in the nivolumab group (13.1% versus 35.1%).

In Phase III study of gefitinib compared with intravenous methotrexate in previously treated four hundred eighty-six patients with recurrent SCCHN were randomly assigned to oral gefitinib 250mg/day, gefitinib 500 mg/day, or methotrexate 40mg/m² intravenously weekly.²⁸ Neither gefitinib 250 nor 500mg/day improved overall survival compared with methotrexate ($P=.12$ and $P=.39$, respectively). Median survival with gefitinib 250mg was 5.6 months, compared to, gefitinib 500mg (6.0 months), and methotrexate (6.7 months). Patients with platinum-resistant disease had a survival advantage when given methotrexate.

In Eastern Cooperative Oncology Group Trial, 270 Patients with recurrent or metastatic SCCHN with ECOG performance status of 2, or patients with ECOG performance status of 0 to 2 but were previously treated with chemotherapy, were randomly assigned to receive weekly docetaxel plus either placebo (arm A) or gefitinib 250 mg/d, orally (arm B) until disease progression.²⁹ The study was closed early at interim analysis (arm A, $n=136$; arm B, $n=134$). Median overall survival was 6.0 months in arm A versus 7.3 months in arm B ($P=.60$). An unplanned subset analysis showed that gefitinib improved survival in patients younger than 65 years (median 7.6 v 5.2 months; $P=.04$). Also, there was a trend for improved survival in patients with c-MET wild-type (5.7 v 3.6 months; $P=.09$) regardless of treatment. Grade 3/4 toxicities were comparable between the two arms.

LUX-Head & Neck 1 trial³⁰ is an open-label, phase 3, randomised controlled trial conducted in 101 centres in 19 countries between Jan 10, 2012, and Dec 12, 2013. Patients with recurrent, metastatic, or both who had progressed on or after first-line platinum-based therapy, who were not amenable for salvage surgery or radiotherapy, were randomly assigned in a 2:1 ratio to receive oral afatinib (40mg/day, $n=322$) or intravenous methotrexate (40mg/m² per week, $n=161$). After a median follow-up of 6-7 months, progression-free survival was longer in the afatinib group than in the methotrexate group (median 2-6 months for the afatinib group vs 1-7 months for the methotrexate group; $p=0.030$) and had a manageable safety profile. These findings provide important new insights into the treatment of this patient population and support further investigations with irreversible ERBB family blockers in HNSCC. Erlotinib, is a reversible EGFR TKI and has demonstrated modest activity as monotherapy³¹ and lapatinib,³² a dual EGFR/human epidermal growth factor receptor 2 (HER2) inhibitor failed to show any benefit in recurrent/metastatic setting.

Dacomitinib, another irreversible pan-ErbB inhibitor (EGFR, HER2, and HER4), demonstrated a modest response rate of 12.7% and median PFS and OS times of 12.1 and 34.6 weeks, respectively, in a phase II study of dacomitinib monotherapy in 69 patients with R/M HNSCC.³³ Another molecule which has gained recent momentum is Pembrolizumab (Keytruda), an anti-programmed death 1 receptor antibody. The FDA granted accelerated approval to pembrolizumab for

patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy in August 2016 based on results from the open-label phase Ib KEYNOTE-012 trial.³⁴

The phase II KEYNOTE-055 trial³⁵ -reported by Bauml et al confirms the activity of pembrolizumab in previously platinum-and cetuximab treated recurrent or metastatic squamous cell carcinoma of the head and neck. Among 171 patients treated, 75% received two or more prior lines of therapy for metastatic disease. Median progression-free survival was 2.1 months, and median overall survival was 8 months. 82% were PD-L1 positive, and 22% were HPV positive. Response rates were similar in all HPV and PD-L1 subgroups.

But Pembrolizumab did not meet the primary endpoint of overall survival in patients with previously-treated recurrent or metastatic head and neck squamous cell carcinoma in the phase III KEYNOTE-040 trial.³⁶ KEYNOTE-048, a phase III trial comparing pembrolizumab with platinum-based chemotherapy plus 5-FU and cetuximab, or in combination with platinum-based therapy and 5-FU as a frontline treatment for patients with recurrent or metastatic HNSCC is ongoing.

In conclusion chemotherapy+cetuximab improves overall survival when compared to chemotherapy alone for recurrent/metastatic head and neck carcinoma and is approved as first line treatment modality. Nivolumab improves survival in platinum refractory disease compared to single agent chemotherapy. Other agents in the second line setting, Gefitinib has shown comparable results to methotrexate and Afatinib has shown better progression free survival compared to methotrexate.

Mechanisms of resistance to cetuximab

Randomized trials by Bonner et al.⁴ and EXTREME trial have demonstrated that many HNSCC patients do not respond to cetuximab, despite HNSCC being overwhelmingly EGFR-positive. In HNSCC, the mutations and alternate pathways theorized to possibly

contribute to anti-EGFR resistance are numerous, including mutations in the extracellular domain (EGFRvIII) and tyrosine kinase domain, K-ras and H-ras, mutations in epithelial-mesenchymal transition such as increased vimentin expression, decreased E-Cadherin expression, decreased Claudins 4 and 7 expression, alternate pathways such as Cyclin D1 upregulation, PTEN mutations, PI3KCA mutations, Akt Amplification³⁷ Elucidating these mutations and alternate pathways will be vital going forward in order to 1) combine anti-EGFR therapy synergistically with other agents and 2) predict who will respond to anti-EGFR therapy ie begin to personalize HNSCC treatment.

Another potential cause of cetuximab resistance is the EGFR variant III (EGFRvIII) a mutation found in 42% of HNSCC tumors which results in a ligand-independent activation of the receptor.³⁸ EGFRvIII is not required to dimerize with another receptor for activation and signals downstream only through the PI3K pathway, unlike wild-type EGFR (wtEGFR).³⁹ The binding affinity of cetuximab to EGFRvIII is much lower compared to wtEGFR, providing an explanation for resistance of some HNSCC tumors to cetuximab. Furthermore, EGFRvIII mediates tumor cell migration and invasion by increased STAT3 activation and induction of HIF1- α , contributing to cetuximab resistance in HNSCC. Targeting this unique structure of EGFRvIII has recently become the focus of study in overcoming this resistance.^{40,41}

Most consistent marker of response to EGFR inhibitors is clinical: development of acneiform rash. In the Bonner trial, at 5-year follow up, patients in the cetuximab arm with a prominent acneiform rash (grade 2-4) had a significantly longer overall survival than those with a mild rash (68.8 vs. 25.6 months). This may implicate the acneiform rash as a biomarker for optimal outcome with cetuximab.⁴ In addition to the aforementioned Bonner trial, numerous authors have reported a correlation between development of rash and response to EGFR inhibitors in various cancers including HNSCC, colorectal cancer, gynecologic and lung cancer (Table 5).

Table 5 Current trials (phase II) combining cetuximab and other agents in the treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)

Trial	Regimen	Phase	Sample size	Target
NCT01040832-EMD 1201081 with cetuximab in second-line cetuximab-naïve in recurrent or metastatic squamous HNSCC	Cetuximab weekly vs. cetuximab weekly+EMD 1201081 0.32mg/kg weekly	II	104	TLR9
NCT00409565—Cetuximab and bevacizumab in recurrent or metastatic HNSCC	Cetuximab weekly+ bevacizumab 15mg/kg q3 weeks	II	48	VEGFR
NCT01256385-Temsirolimus with or without cetuximab in patients with recurrent and/or metastatic head and neck cancer who did not respond to previous therapy	Cetuximab+temsirolimus weekly vs. temsirolimus weekly	II	80	mTOR
NCT01316757-Carboplatin, paclitaxel, cetuximab, and erlotinib In metastatic or recurrent HNSCC	Cetuximab, paclitaxel, carboplatin q21 days + daily erlotinib (starting in course 2)	II	43	EGFR
NCT01015664-Cisplatin, cetuximab and temsirolimus in recurrent or metastatic HNSCC	temsirolimus weekly (10, 15 or 25 mg), cisplatin month1+ cetuximab weekly	II	56	mTOR
NCT01252628-PX-866 and Cetuximab	cetuximab+PX-866 vs. cetuximab	I/II	178	PI3K
NCT01087970-Pemetrexed, cetuximab and carboplatin or cisplatin in recurrent or metastatic HNSCC	Pemetrexed, cetuximab + carboplatin or Cisplatin	II	108	TS, DHFR, GARFT
NCT01283334-Carboplatin, cetuximab and RAD001 in advanced HNSCC	Carboplatin, cetuximab + RAD001	II	48	mTOR

Note: Taken from clinicaltrials.gov.

Complications of molecularly targeted therapy and management

Targeted therapy is not the one without side effects. Rash is the most common side effect and has been encountered with 70% to 80%, of the patients. However severity of the reaction may vary with grade

3rash in 10% of population. They start with Acne form reactions, over time recedes from face and chest to hands and feet and hairline, can also cause Nail dystrophy and fissures. Hypersensitivity reactions have been reported in: 3% to 5% of population. Other significant toxicities are cardiotoxicity (<5%) and hypomagnesemia. Diarrhoea is the other common side effect seen with oral EGFR TKIs (Table 6).⁴²

Table 6 Skin reaction algorithm

Mild	Continue EGFR inhibitor at current dose and monitor for change in severity	Topical hydrocortisone 1% or 2.5% cream and/or Clindamycin 1% gel	Reassess after 2 wks; if reactions do not improve, proceed to next step
Moderate	Continue EGFR inhibitor at current dose and monitor for change in severity; continue treatment of skin reaction	Hydrocortisone 2.5% cream or Clindamycin 1% gel or Pimecrolimus 1% cream plus Doxycycline 100mg BID or Minocycline 100 mg BID	Reassess after 2 wks; if reactions do not improve, proceed to next step
Severe	Reduce EGFR inhibitor dose per label and monitor for change in severity; continue treatment of skin reaction	Treat as above plus Methyl prednisolone dose pack	Reassess after 2 wks; if reactions worsen, dose interruption or discontinuation may be necessary

Summary

Cetuximab in combination with platinum-based combination chemotherapy is superior to chemotherapy alone in patients with recurrent or metastatic HNSCC, and is recommended to improve overall survival, progression-free survival, and response rate. Nivolumab improves survival in the second line setting. Patients with HNSCC should continue to be offered clinical trials of novel agents aimed at improving outcomes.

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Conflict of interest

The author declares no conflict of interest.

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